

Bypassing Medicine to Treat Diabetes

By altering the gut's production of hormones, gastric bypass surgery may be able to eliminate type 2 diabetes. But scientists worry that this radical operation can also cause dangerously low blood sugar

IN 1980, BARIATRIC SURGEON WALTER Pories of East Carolina University School of Medicine in Greenville, North Carolina, performed his first gastric bypass surgery on an obese patient with type 2 diabetes, then a second, then a third. He noticed right away that the patients no longer needed insulin. Family doctors confirmed that what Pories had considered a transient phenomenon seemed like something more: Each person's diabetes had disappeared, even before they'd lost much weight. Pories was convinced that the doctors had erred. "I said, 'You guys don't know how to work up diabetes. Diabetes is an incurable disease.'" After the fourth patient, Pories and an endocrinologist took matters into their own hands. "We marched right down to the lab, very self-righteous," and accused the lab employees of incorrectly measuring blood sugar levels. ("If you're a doctor, you like to blame other people," Pories explains.)

As the number of patients with vanishing diabetes mounted, Pories recognized that the effect was real. Still, the concept that diabetes could be reversed surgically was so outlandish, he says, that "we didn't dare publish" the results. Instead, Pories began tracking his patients. In 1995, he reported in the *Annals of Surgery* that among 146 people with diabetes who had had the surgery in the past 14 years, 121, or 83%, had quickly become diabetes-free. The result was far superior to that achieved by any other treatment at the time—or now.

"The surgical world noted that paper," says endocrinologist David Cummings of the University of Washington, Seattle. But it took "another 10 years for the rest of us" to catch up, he says. Now, endocrinologists are beginning to pay close attention to the effects of gastric bypass surgery, which had long been a backwater of medicine, in part because obesity was not considered a genuine disease.

As America and other countries confront surging rates of obe-

sity, with few treatments that shrink the widest waistlines, the surgery's popularity is soaring. The most common form in the United States, Roux-en-Y gastric bypass, was performed on more than 120,000 people in 2007, according to estimates. That's almost double the number 5 years ago. Doctors often learn from their patients, and the hundreds of thousands of people who have had gastric bypass surgery are now prompting an overhaul in our understanding of metabolism and diabetes. Scientists are also going back to animals to figure out the impacts of the procedure. They are finding that the surgery's rerouting of the intestines and closing off of much of the stomach appears to have drastic effects on gut hormones and disease, independent of the weight loss that accompanies it.

These effects can also have dire consequences. Beginning in 2000, F. John Service, an endocrinologist at the Mayo Clinic in

Rochester, Minnesota, began seeing patients with some alarming symptoms: confusion, abnormal behavior, seizures, and unconsciousness. In each case, the culprit was a low level of blood sugar that struck after eating, which is when it rises in healthy people. Every patient, it turned out, had undergone gastric bypass surgery months or years earlier. The Mayo Clinic now sees at least two new patients a month with this unusual hypoglycemia disorder, which was the topic of a meeting at the Joslin Diabetes Center in Boston earlier this month.* As a last resort, surgeons have removed part or even all of the pancreas, which churns out insulin, from many of these patients.

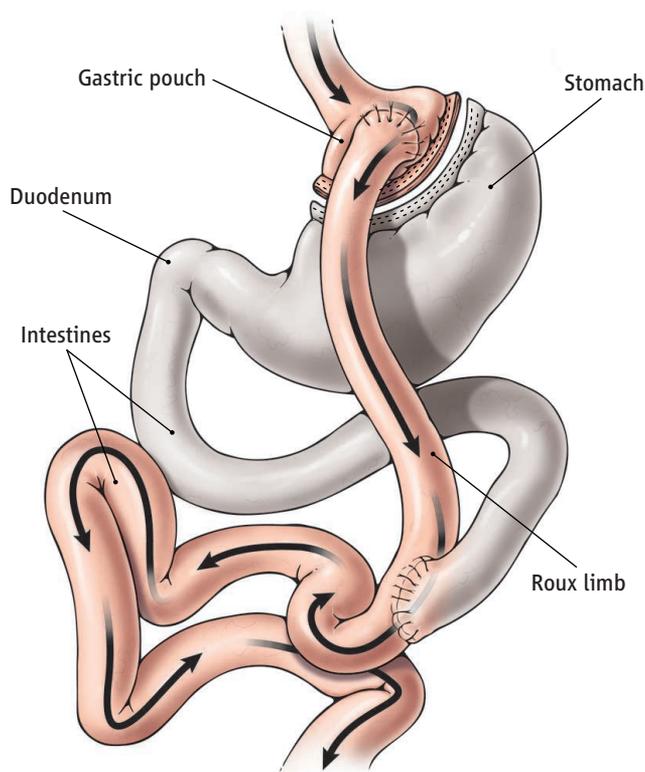
How to decipher and harness the surgery's metabolic effects is prompting much debate. On the one hand, some surgeons are already operating on less obese people with diabetes as a treatment for that disease. But others would prefer to wait until the science catches up, especially because the surgery isn't harmless, with a death rate ranging from 0.1% to 2%, depending on where it's performed. "Surgeons have for too long acted in a vacuum. ... Most of them aren't

thinking about the mechanisms of what they're doing," says John Dixon, an obesity researcher at Monash University in Melbourne, Australia. "But we need to dissect out" what's happening in these patients.

Early clues

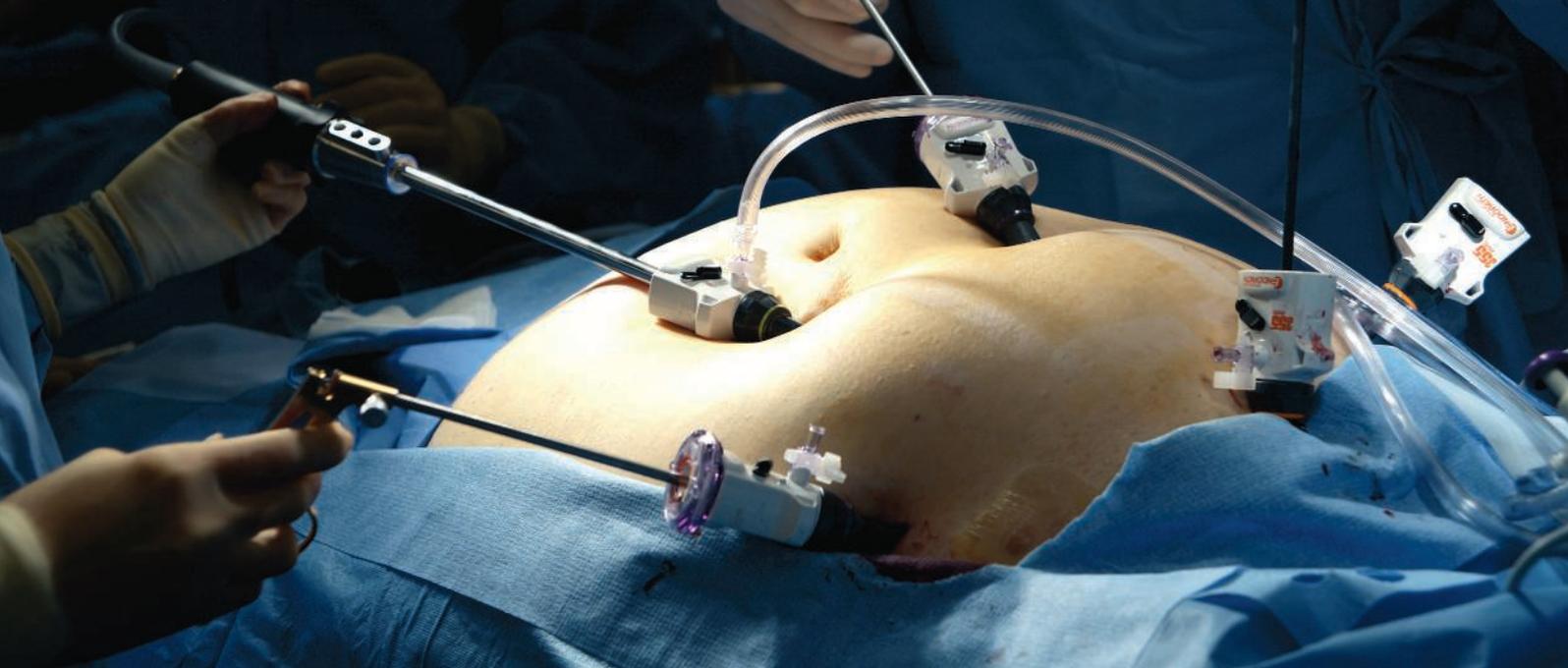
Gastric bypass was inspired by similar intestinal operations employed for ulcers and gastric cancer that induced dramatic and enduring weight loss and were reported to reverse diabetes as far back as the 1950s. "As soon as we started doing the operation, we were aware of the fact that before the patients got out of the hospital, they no longer needed insulin," says Edward Mason, a retired surgeon from the University of Iowa in Iowa City who developed the procedure for weight loss. Most current forms of gastric bypass,

*Hyperinsulinemic Hypoglycemia Following Gastric Bypass: Pathogenesis and Treatment Symposium, Boston, Massachusetts, 7 April.



Unintended effects. Roux-en-Y gastric bypass surgery reduces the stomach to a fraction of its original size and skips past part of the small intestine, which causes profound metabolic changes in the gut.

Beyond fat. From the early days, doctors recognized that for many patients, diabetes vanished after gastric bypass.



and Mason's original operation, have one element in common: A newly created exit from the stomach is reconnected to a piece of small intestine a few feet lower down, "bypassing" the upper portion of the small intestine. In addition, the stomach is drastically restricted, by about 95%. (Another weight-loss surgery, gastric banding, seals off most of the stomach but leaves the intestines intact and is not considered gastric bypass.) Today, most gastric-bypass patients shed 30% of their body weight and keep it off.

Mason, now 87 years old, recalls that he and others explained away the reversals of type 2 diabetes because their patients weren't eating right after surgery, which would lower blood glucose levels and, in turn, their need for insulin. (The surgery does not have the same effect on type 1 diabetes, in which afflicted individuals cannot produce insulin.) But Pories's study years later slowly began to convince people that something more fundamental was occurring.

Almost a decade later, a second report strengthened the case. In 2003, Philip Schauer, a bariatric surgeon now at the Cleveland Clinic in Ohio, published follow-up data from 1160 obese people who in the preceding 5 years had undergone Roux-en-Y gastric bypass, which gets its name from a French surgeon who developed the technique. Of the 191 people with diabetes or impaired glucose metabolism who could be tracked down, 83%, precisely the figure reported by Pories,

no longer had the problem.

Although impressive, it's not yet clear if these success rates will hold up in clinical trials. These are "typically the observations of a single surgeon or group of surgeons" and "very anecdotal," says David D'Alessio, an endocrinologist at the University of Cincinnati in Ohio.

Getting at biology

After years of absence, science is slowly making inroads into gastric bypass surgery. "The development of the field was not based on real research," says Francesco Rubino, a bariatric surgeon at Weill Cornell Medical College in New York City. "That has tarnished the field somewhat."

Recently, however, a growing number of studies are suggesting that the surgery has a profound effect on gut hormones, which could explain its impact on appetite, diabetes, and the low blood sugar that's turning up. One of the first clues emerged in 2002, when Cummings looked into a well-recognized oddity. Gastric bypass restricts the stomach, forcing people to eat smaller meals. One might then expect "that people would be compelled to sip milkshakes all day long," says Cummings. That's not what happens. Many move away from calorie-dense foods altogether.

Curious, Cummings began examining levels of ghrelin, a hormone produced mainly by the stomach that stimulates appetite. Most people have peaks and valleys in ghrelin levels throughout the day as they consume meals and then become hungry again. In those who've had gastric bypass, Cummings found, ghrelin levels in blood were low and changed little all day, suggesting that something about the surgery dampens ghrelin production and hence appetite.

The role this plays in diabetes resolution has not been firmed up, and researchers are

now more closely examining how gastric bypass affects other hormones. Rubino's work, for example, has focused on the intestines, which produce a different suite of chemicals and hormones from those the stomach churns out. In 1999, Rubino turned to rats to examine whether the surgery's effects on diabetes were due to calorie restriction and weight loss alone. He tried to tease apart

distinct features of his "patients"—the rats, in this case—and different features of surgery. When performed on lean animals with type 2 diabetes, gastric bypass had the same positive effects on the diabetes as in obese ones, suggesting that weight loss was largely irrelevant. Furthermore, Rubino performed the

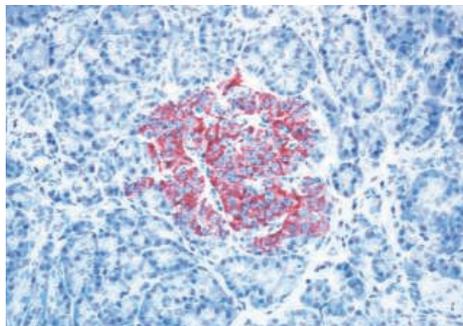
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MONASH UNIVERSITY

intestinal bypass portion of the operation, skipping past the duodenum and the jejunum that link up to the stomach, but leaving the stomach intact. There was a “direct antidiabetic effect,” he says.

Rubino’s rat work dovetails with a popular theory: that a hormone produced by the intestines called glucagon-like peptide 1 (GLP-1) lies behind the vanishing diabetes in many gastric bypass patients—and may be linked to the hypoglycemia that later strikes others, most of whom did not have diabetes before the surgery. The GLP-1 theory is that the small intestine goes into overdrive making hormones in gastric bypass patients. Because of the surgical rerouting, food “empties directly into this part of the intestine that it normally wouldn’t see at that stage” of digestion, says Mary-Elizabeth Patti, an endocrinologist at the Joslin Diabetes Center.

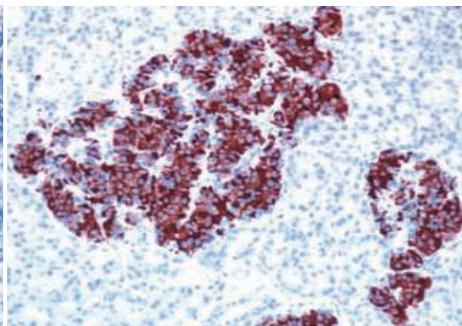
In healthy people, GLP-1 has a variety of effects, including increasing insulin secretion,



might be due to other nonpancreatic effects.

When Service and his Mayo colleagues examined the pancreatic tissue removed to help their hypoglycemic patients, they noted islets that appeared larger than normal. Joslin researchers have also reported an excess of insulin-producing cells in three hypoglycemic patients, two women and a man, who had a portion of their pancreases removed. The hypoglycemia is “diabetes reversal in people who don’t have diabetes,” says Patti.

D’Alessio is now trying to study GLP-1 in people who have had gastric bypass surgery and are suffering from hypoglycemia to determine whether the hormone might induce such pancreatic changes. But not everyone agrees that gastric bypass surgery alters the pancreas. Peter Butler, an endocrinologist at the University of California, Los Angeles, examined the pancreases from Mayo at Service’s request and found that they looked like pancreases



Insulin overload? An islet in the pancreas (*left*, red) appears larger in a gastric bypass patient (*right*) who suffers from dangerously low blood sugar, but scientists dispute whether the surgery changes that organ.

and a diabetes drug on the market, called Byetta, mimics the effects of GLP-1. Physiologist April Strader of Southern Illinois University in Carbondale is now performing an intestinal surgery in rats that leaves the stomach intact and prompts the animals to secrete more GLP-1. Strader is examining whether that in turn causes proliferation of insulin-producing cells in the pancreas.

Linking the good and bad

GLP-1’s impact on the pancreas may also explain the hypoglycemia originally seen by the Mayo Clinic. One sharp contrast between the disappearance of diabetes and the hypoglycemia stemming from the surgery is that the former occurs immediately or within weeks, whereas the latter takes several years to show up. At the Boston meeting, the 40 or so surgeons, endocrinologists, pathologists, and others gathered there admitted that they couldn’t explain this but wondered whether changes to the pancreas over time generated the low-blood-sugar problems, whereas diabetes improvement

from obese individuals. He attributes this difference of opinion to his more extensive analysis, which did not identify an upsurge in insulin-producing cells.

Butler did make one intriguing find, however. Obese people tend to produce more insulin over time to accommodate the growing amount of tissue that requires the hormone. Based on the appearance of the islet cells, Butler deduced that the gastric bypass pancreases hadn’t made the adjustment to their host’s new weight: They were still producing just as much insulin as before the surgery, effectively increasing the insulin available. That this occurs after meals would make sense, because this is when the pancreas normally releases extra insulin. In these patients, the insulin they secrete would far exceed what’s needed.

Stephen Bloom, an obesity researcher at Imperial College London, notes that it’s far from clear whether GLP-1 has the same effect on human pancreases as it does on those of rodents. Furthermore, the small intestine secretes dozens of hormones, many of them poorly understood. “It’s still too

soon to rule out everything else,” says Strader. Rubino agrees that researchers need to think expansively. Instead of largely undigested food stimulating hormone secretion from the intestines it’s dumped into, it’s possible that when food does not touch the walls of the duodenum, as happens in gastric bypass, that has hormonal effects of its own. Rubino says his recent findings in animals suggest such antidiabetic effects.

Surging popularity

As research picks up pace, gastric bypass surgeries continue unabated, and some surgeons, particularly outside the United States and Europe, are beginning to operate on less obese patients with diabetes. Bariatric surgery is “kind of the Wild West,” says D’Alessio. There’s “huge demand, no regulation, everybody’s got their own operation, [and] patients are willing to do whatever it takes to get it.”

Currently, U.S. National Institutes of Health guidelines recommend that gastric bypass surgery be considered only for people who have a body mass index (BMI) of at least 35. (A BMI of 18.5 to 25 is considered normal.) At a meeting in Rome last year, 78% of attendees supported lowering the limit to a BMI of 30 for those with diabetes. Should the number be even less? “We need more data to know if a lower bar is okay or if there should be any bar at all” when the goal is diabetes treatment, says Cummings.

But many still view gastric bypass as extreme therapy for diabetes. Some who undergo the operation have serious problems, such as infections, gallstones, and hernias, that can require additional surgery. And given the time lag between gastric bypass and the severe hypoglycemia that Service, Patti, and others are just now documenting, no one knows how prevalent the side effect will be nor how much such patients will affect the cost-benefit analysis. The death rate from gastric bypass surgery also scares many diabetes researchers. “We had a death in a 28-year-old recently; she had a complication but didn’t want to come to the hospital,” says Bloom. “When you see that and have to go to the funeral, you don’t think it’s such a harmless procedure.”

Yet type 2 diabetes isn’t harmless, either, contributing to more than 1 million deaths worldwide each year. “There is a barrier we need to get over” in considering gastric bypass as a diabetes treatment, says Rubino. He points to a paper published last summer, concluding that the surgery reduces diabetes deaths by 92%. “It’s the most profound effect in terms of mortality from diabetes ever reported,” Rubino says. “What is the price of that?”

—JENNIFER COUZIN